Role of Models in the Quality by Design (QbD) Paradigm: Regulatory Perspective

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Outline

- Definition of a model and types of models
- Examples of models from some QbD based applications
- Considerations for models
- Considerations for submissions
- Concluding remarks

Introduction

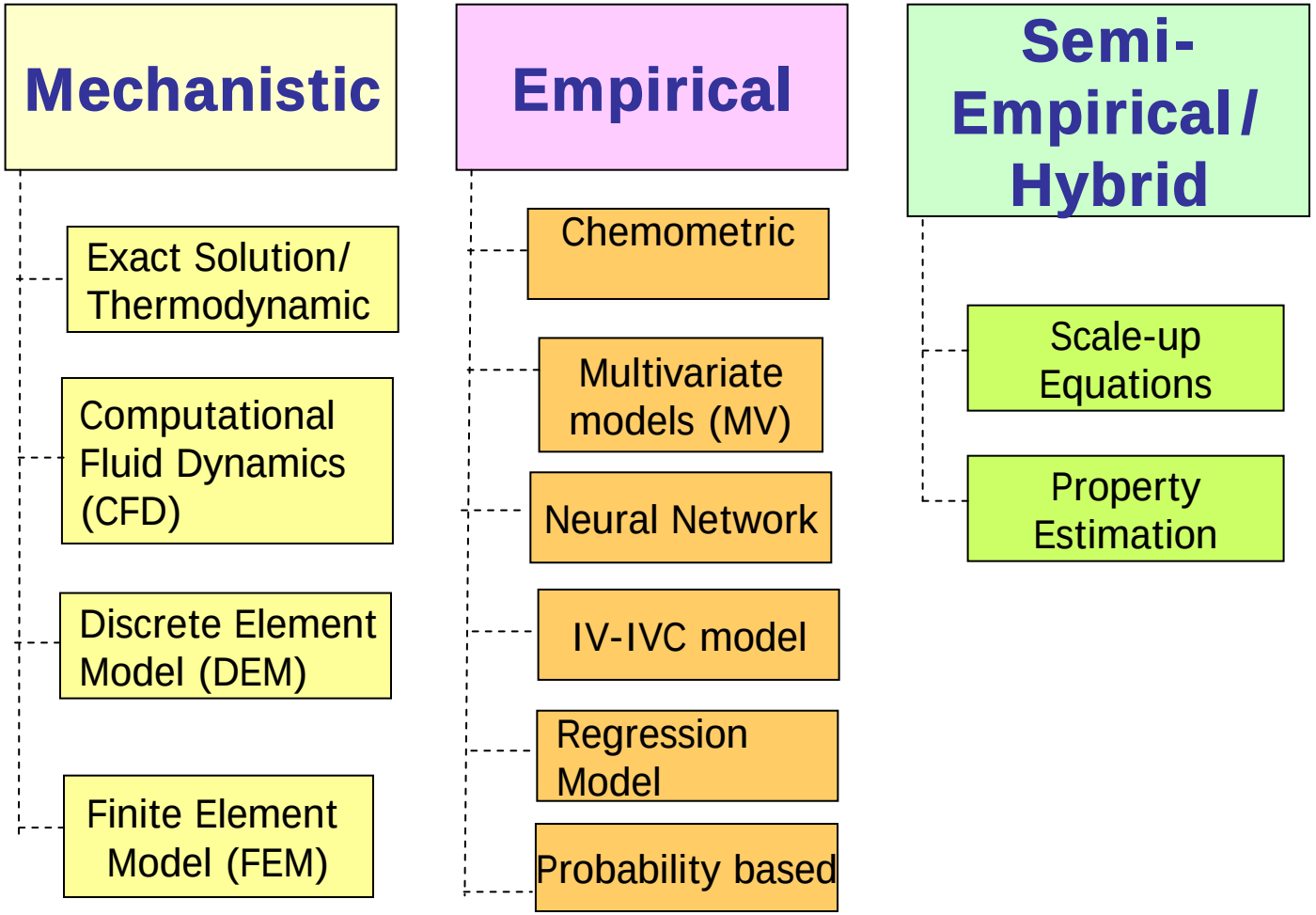
What is a Model?

A model is a representation of an underlying physical/chemical phenomena

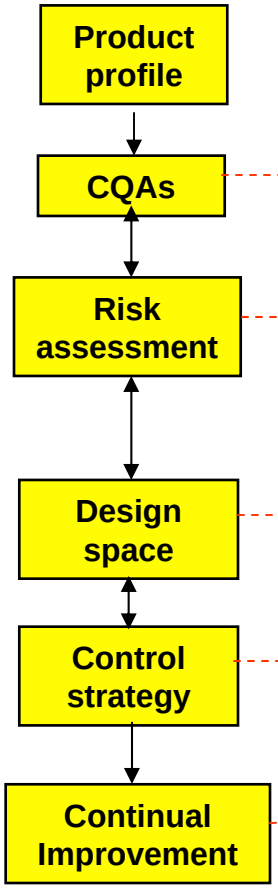
Advantages of Models:

- Enhanced process understanding
  - Allows decision making
- Reduction of number of experiments
- Improvement of productivity and product quality

Types of Models and Methodologies (partial list)



Modeling Strategies in the QbD Paradigm



IV-IVC models to establish in-vitro dissolution criteria based on in-vivo performance

- Failure Mode Effect Analysis (FMEA)
- Mechanistic model to assess impact of parameters

- Regression correlations based design space
- Uncertainty analysis for edge of failure estimation
- Scale up models to scale up/down design spaces

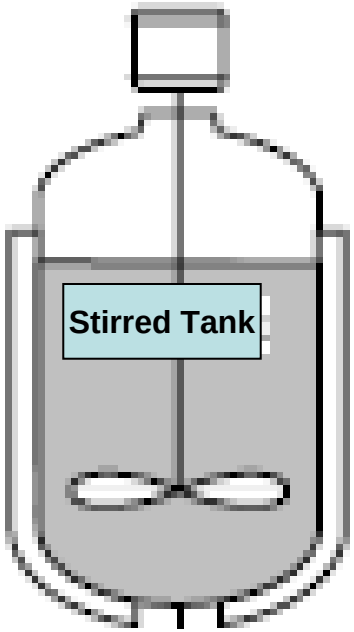
- Model based specifications
- Multivariate models to implement Real Time Release Testing (RTRT)
- Chemometric models associated with PAT tools

Multivariate Statistical Process Control (MSPC) based model

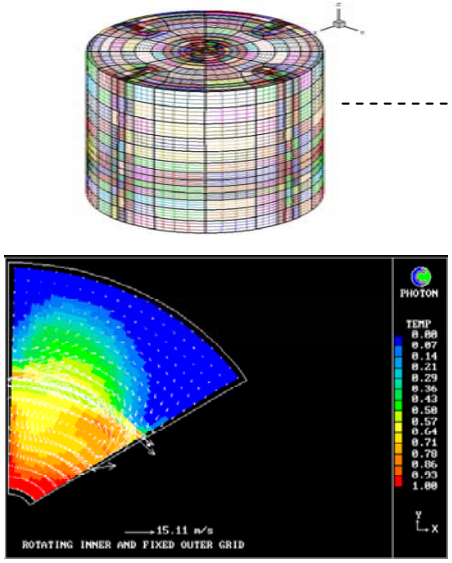
Models can be used at every stage

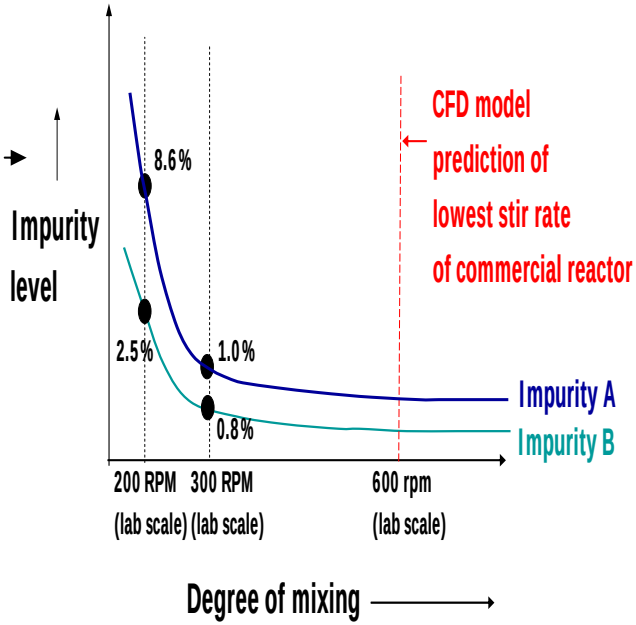
CASE STUDIES FROM RECENT APPLICATIONS

Example of a Model for Risk Assessment



Computational Fluid Dynamics
Stirred Tank Example





To determine if mixing speed in the stirred tank reactor has an impact on impurity level

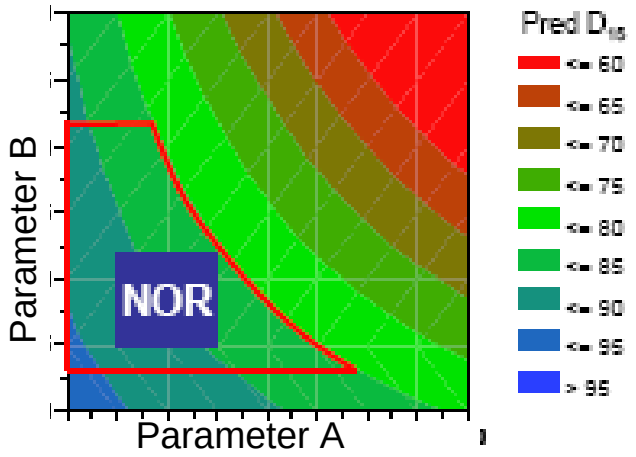
CFD model of stirred tank

Model showed that adequate mixing is attained at all settings at commercial scale.

Thus, mixing speed is delineated as a Non Critical Process Parameter (NCPP)

Example of a Model for Defining Design Space

Design space represented as a contour space on the basis of DOE data



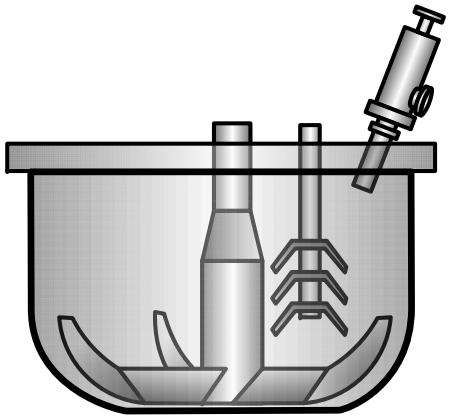
Design space for dissolution in terms of a regression correlation

Prediction algorithm:

$$Diss = 108.9 - 11.96 \times API - 7.556\times10^{-5} \times MgSt - 0.1849 \times LubT - 3.783\times10^{-2} \times Hard - 2.557\times10^{-5} \times MgSt \times LubT$$

Adapted from ICH QIWG training slides, Washington DC, October, 2010

Example of a Model for Scaling up Design Space



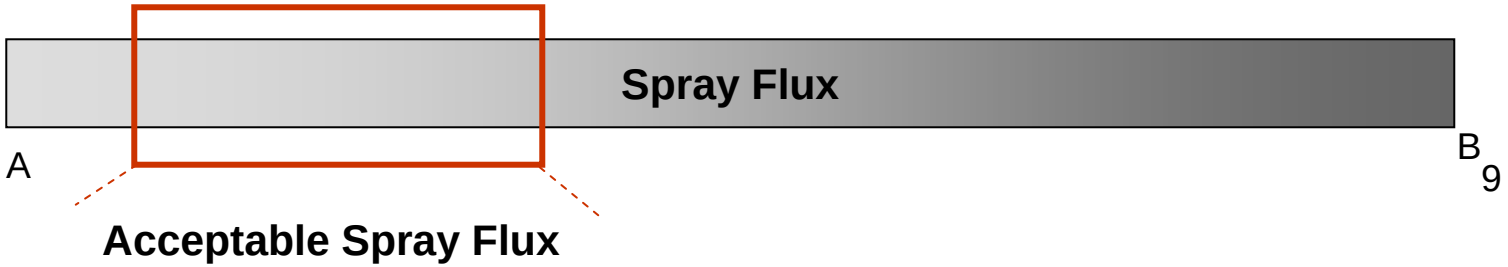
High Shear Granulator (HSG)

Impact of some process parameters for HSG (i.e. liquid flow rate, binder drop size and powder flux through spray zone) represented in terms of a Dimensionless Number: **Spray Flux**

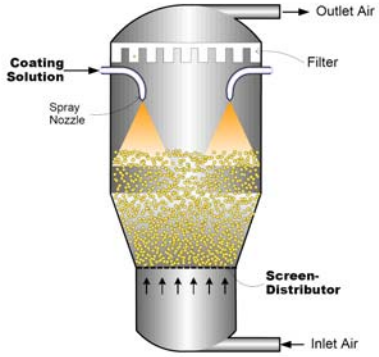
Spray Flux: *Measure of area wetted by drops from spray nozzle to powder flux through spray zone*

Multivariate DOE to study granulation at pilot scale (inputs: amount of granulation liquid, impeller speed, granulation time)

Analysis of DOE data used to define a **scale invariant** design space in terms of **Acceptable Spray Flux**



Example of a Model for Control Strategy: Part I Model Based Specifications



DOE on Spray Dryer.
Ranges determined for spray dried product CQA e.g. bulk density, PSD

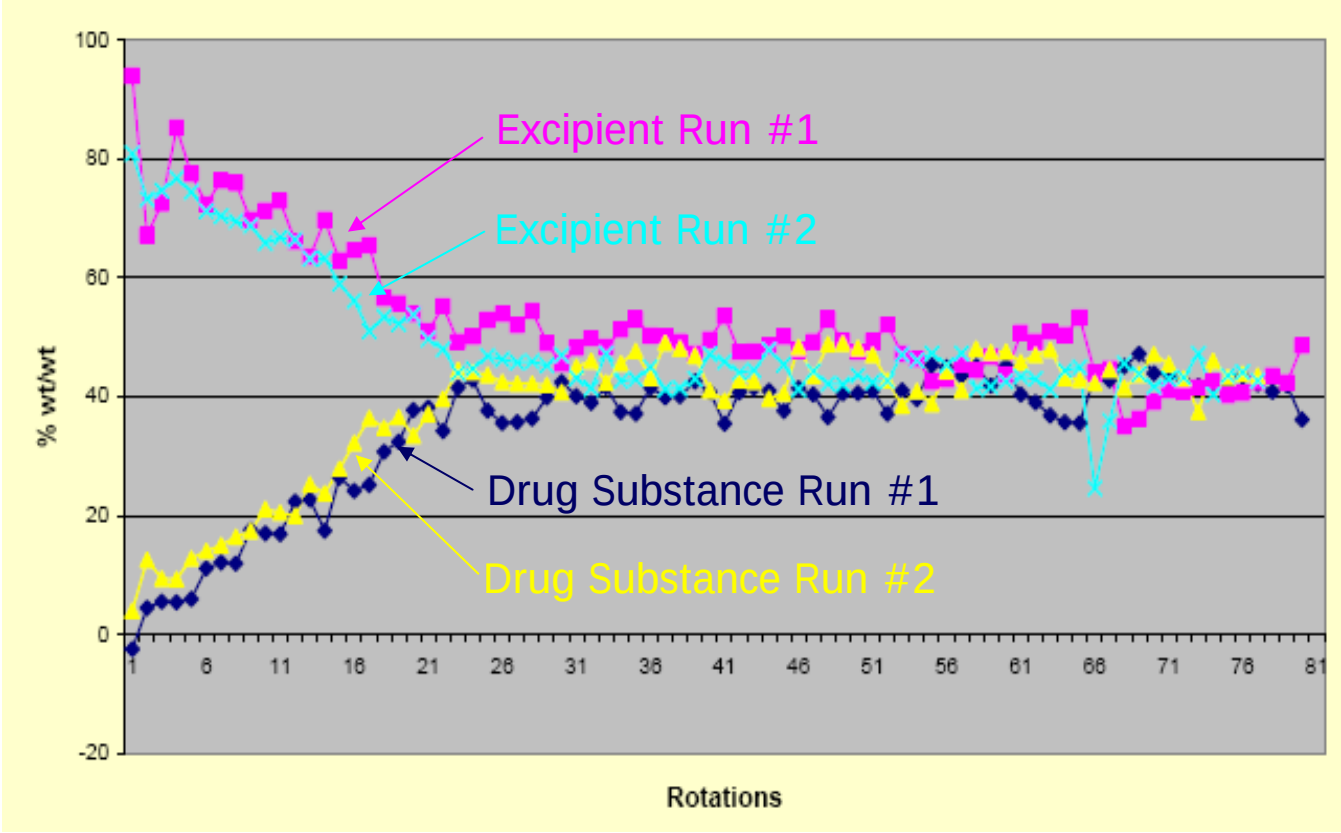
DOE on Tablet Press
Inputs included ranges of spray dried product PSD and bulk density
Measured response: Dissolution
Regression model: Dissolution = f (bulk density, PSD, …)

Regression model used to set Acceptance Criteria for Spray Dried product PSD

Part I – Continued: Example of Model based Specification for Spray Dried Dispersion

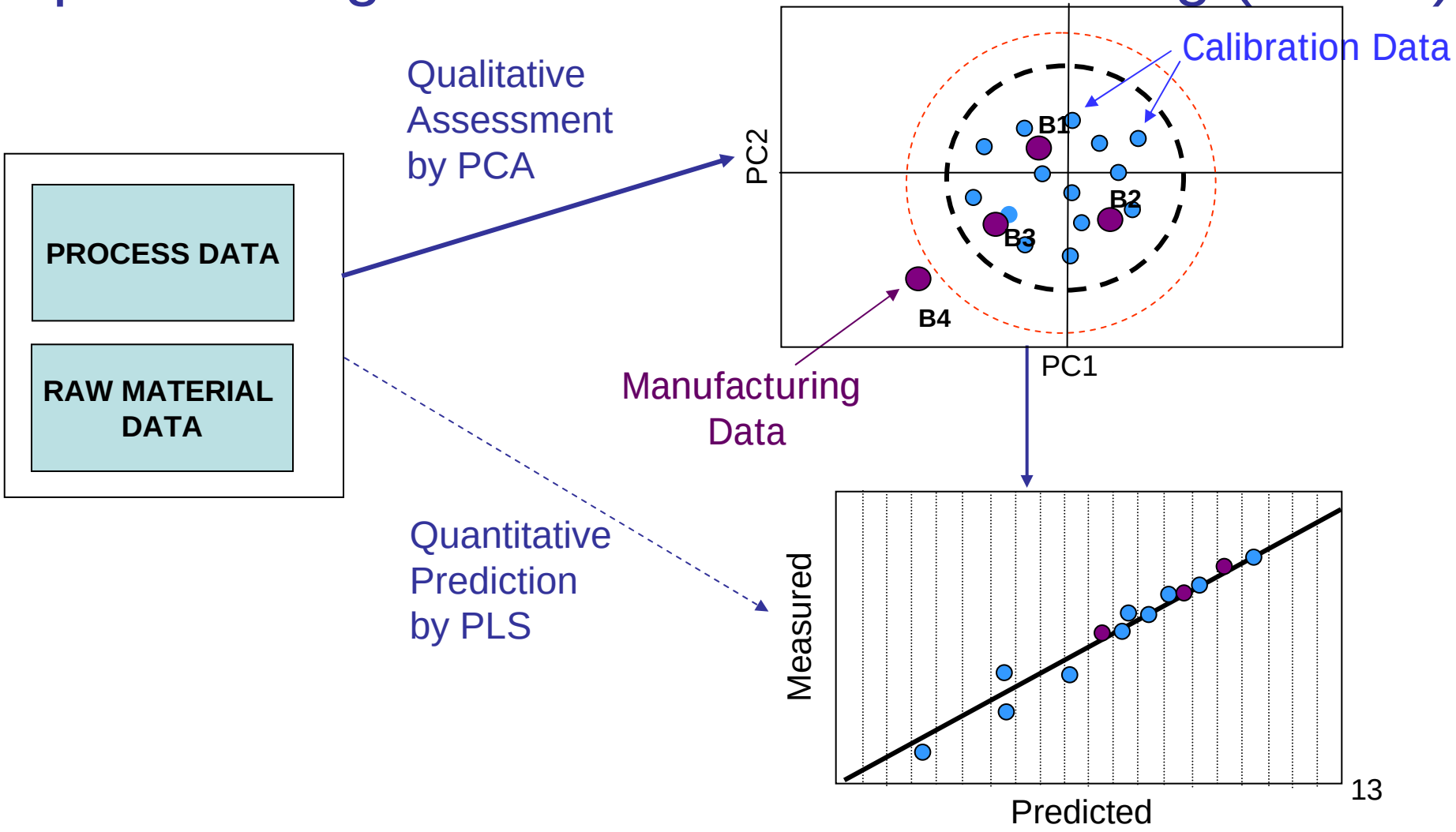
Title of Test	**Test Method** *(method numbers would also be included)*	**Acceptance Criteria**
Bulk Density (BD)	USP <616>	0.3-0.5 g/cc
Particle size	Laser Diffraction	d_{50} NLT 60 μm AND d_{90} NMT 110 μm AND NMT $\left(\frac{6.5+30.5BD}{2.05BD-0.223}\right)$ μm

Example of a Model for Control Strategy: Part II Chemometric Model for Blend Uniformity



Uniformity of excipients and blend determined by on-line process monitoring by NIR

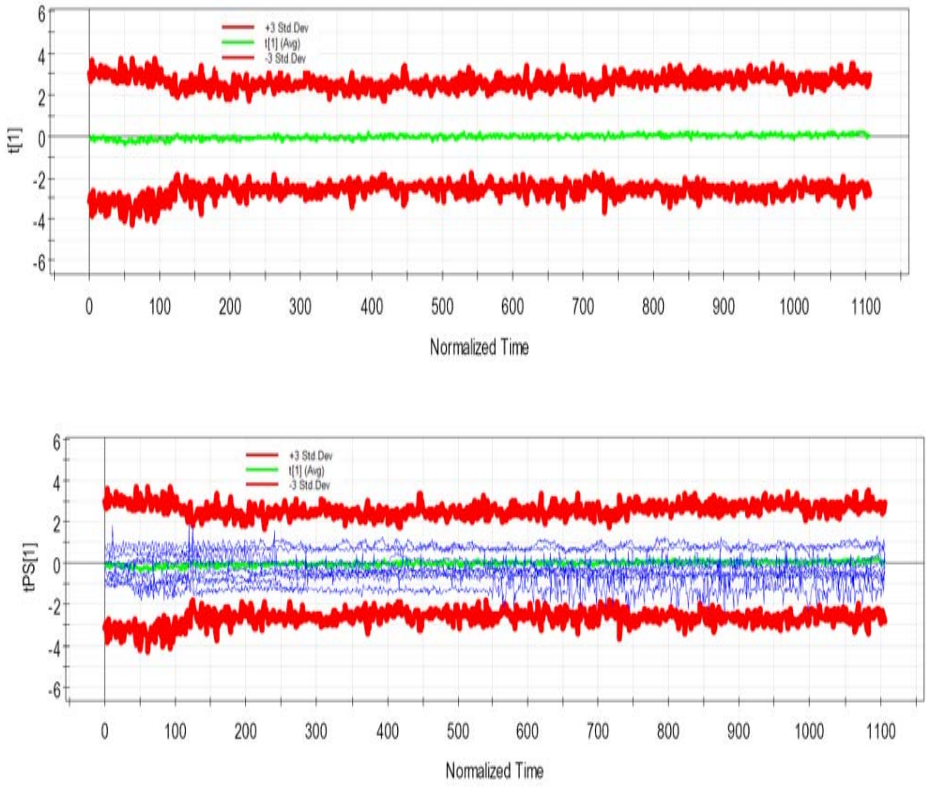
Example of a Model for Control Strategy: Part III Implementing Real Time Release Testing (RTRT)



Example of a Model for Continual Improvement

- **MSPC (Multivariate Statistical Process Control) model** for a unit operation e.g. compression, built from multiple batch data that were manufactured to produce acceptable quality product

- Compression data from additional batches projected on to the model to demonstrate conformance



General Considerations for Model Building

- Define purpose of model
- Decide on model and experimental approach (mechanistic or empirical)
  - Selection of variables for the model
    - Based on underlying physical-chemical phenomena
  - Selection of sampling methodology
- Understand limitations of model assumptions
  - Allow correct interpretation of model results
  - Include appropriate risk mitigation strategies
- Collect data
  - Data may be collected at laboratory, pilot or commercial scale
  - Variable ranges explored representative of conditions during model implementation
- Develop model relationships
  - Estimate unknown parameters

Considerations for Model Implementation - I

- Evaluate impact of uncertainty in model predictions
  - Use to set operational boundaries
  - Include mitigation steps in control strategy
- Validate model
  - Internal and external validation, as appropriate
  - Models with higher impact to control strategy may require external validation at commercial scale
  - Models used in development typically do not require external validation
- Document model results
  - Plans for model maintenance throughout the product life cycle
  - Continued evaluation and update model, as needed

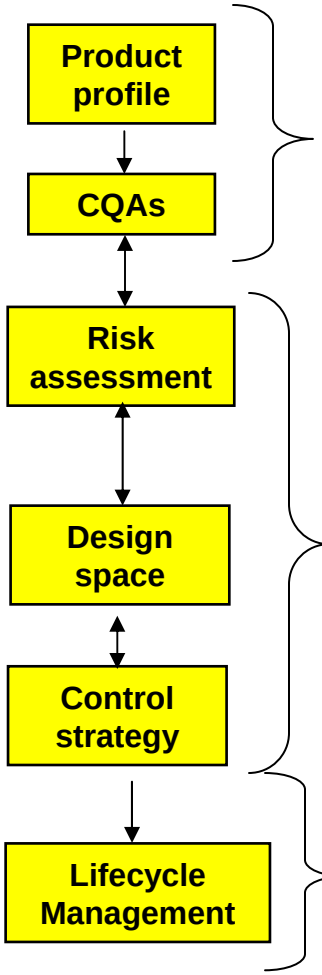
Considerations for Model Implementation - II

- Additional considerations for model validation and maintenance
  - In case of established first principles based models, leveraging prior knowledge to support some validation
  - Setting acceptance criteria relevant to purpose of model
  - Comparison of accuracy of calibration vs. accuracy of prediction
  - Inclusion of the variability anticipated in future routine production in the datasets used for calibration and validation
  - Parallel testing to help support verification at commercial scale
    - Comparison of model prediction with traditional testing results

Considerations for Maintenance of Models

- Develop and document procedures on how to evaluate and update the model
  - How to deal with OOS results
  - Develop criteria for model re-calibration
- Verify or recalibrate the model for process changes:
  - Revised operating ranges
  - Change in raw materials
  - Change in manufacturing equipment or measuring instrument
- Include plans for model maintenance/update in the firm's Quality System
  - Tracking/trending (for process monitoring) included within the Quality System

Examples of Models in the QbD Paradigm



Product Design

- Models to optimize formulation
- IV-IVC models
- Reaction kinetic models

Process Design

- Scale up models to scale up parameters from pilot to commercial scale
- Mechanistic and/or empirical models to define design space
- Chemometric models
- Multivariate models to support RTRT (e.g. surrogate models for dissolution)

Lifecycle Management

- MSPC model for continual improvement

Considerations for Models for Supporting Process Design

- Understand impact of multivariate interactions and potential scale effects at initial scale
- Make predictions based on an appropriate model
  - Incorporate process and/or method uncertainty in the model
- Verify model predictions at commercial scale
  - Verify using measured data
  - Understand model limitations
    - Include appropriate risk mitigation techniques in the control strategy
- Consider plans for model update
  - Example change in raw materials or equipment types

Different Types of Chemometric Models

- Identification methods
  - Differentiate between other compounds or product
  - Include variability between multiple lots
- Quantitative methods
  - Used for assay or concentration measurements
  - Calibration based on a reference method
  - Method performance will not exceed that of the reference method
- Rate of change methods
  - Sometimes used for end-point determination (e.g., blending, drying)
  - Non-calibration method, based on change of variance
  - Probe location can be important (e.g., scale-up)

Additional Considerations for Chemometric Models

- Include as many sources of variability as possible in the calibration model
  - Evenly distributed samples
  - Account for variation in equipment type
  - Adequate justification for choice of spectral wavelength region
- Develop procedures for dealing with OOS
- Understand robustness of model
  - The lowest error is not always the best model!
  - Data pre-processing should have a scientific/physical basis
  - Avoid over-fitting the model
  - Understand limits and assumptions of model

What is Real time Release Testing (RTRT)?

The ability to evaluate and ensure the quality of in process and/or final product based on process data, which typically include a valid combination of measured material attributes and process controls
ICH Q8(R2)

- Could be a component of the Overall Control Strategy
- Relies on:
  - A more extensive product and process understanding
  - Comprehensive product monitoring and process control
  - Robust Quality System

A more modern approach to manufacturing and control

Considerations for Implementing Models for RTRT

- Development of calibration model
  - Include possible variations in raw materials/process conditions to cover the entire design space
  - Use a suitable reference method, if appropriate
- Appropriate validation of model (internal and external)
  - Include an independent dataset for validation
  - Demonstrate for a statistically acceptable number of batches
  - Understand impact of model assumptions and model uncertainty
- Establish a monitoring system to determine when model needs updating or revision

Considerations for RTRT: Specifications

- Still required in an RTRT approach (CFR §314.50(d) and CFR § 211.165(a))
- Can include in-process measurements
- Can include surrogate measurements (e.g., models for dissolution)
- Should be representative of actual measurement
- Alternatives can be included for stability monitoring
- Appropriate statistically based acceptance criteria for large sample sizes

Considerations for Models in Regulatory Submissions

- Documentation is dependent on the intended use of the model and the risk associated with it
- If models are an element of the control strategy
  - Consider approaches for demonstrating suitability of the model throughout the life cycle of the product
  - Details documented within the firm's Quality System

Potential Categorization of Models

- Models may be classified on the basis of their impact on product quality:
  - **High Impact Models**
    - Prediction from the model is the sole indicator of quality of the product, e.g. chemometric model for assay
  - **Medium Impact Models**
    - Important for assuring quality of the product but are not the sole indicators of quality, e.g. model to define a design space
  - **Low Impact Models**
    - Typically used to support process development efforts, e.g. formulation optimization model

Examples of Model Implementation

- Models may be classified on the basis of their intended outcome:
  - **Models for supporting process design**
    - e.g. formulation optimization model, model to define design space
  - **Models for supporting analytical procedures**
    - e.g. chemometric model associated with a NIR based device
  - **Models for process monitoring and control**
    - e.g. Multivariate Statistical Process Control (MSPC) model to support implementation of Real Time Release Testing (RTRT)

Within each of these categories, models may be classified as high, medium or low impact models

Considerations for Submissions – A Reviewer's Perspective

- Depends on the impact of the model to the overall control strategy
- **Low Impact Model**
  - Discussion of how model predictions were used to make decisions during process development
- **Medium Impact Model**
  - Information about: model assumptions, tabular or graphical summary of model inputs and outputs, relevant model equations, statistical analysis where appropriate, comparison of model prediction with measured data, discussion of how elements in the control strategy may help to mitigate uncertainty in the model.
- **High Impact Model**
  - Information about: model assumptions, appropriateness of sample size, data pretreatment, justification of variable selection, tabular or graphical summary of model inputs and outputs, model equations, statistical analysis of data showing fit and prediction ability, rationale for setting of model acceptance criteria, model verification (internal and external), discussion of approaches for model maintenance and update

Regulatory Feedback

- Discuss any ‘novel’ model related concepts with the agency during End-of-Phase II meetings or Pre NDA meetings
  - Data requirement for submissions
  - Approaches for model validation
  - Overall plans for model maintenance
- Refer to the upcoming ICH Points To Consider document on ‘Models in the QbD Paradigm’

Concluding Comments

- Models can support pharmaceutical development as well implementation of modern pharmaceutical manufacturing concepts such as design space, RTRT, continual process monitoring etc
- Role of models in pharmaceutical development and manufacturing is an evolving subject
  - More understanding is expected to be gained over time
- ONDQA is willing to discuss modeling related concepts with applicants prior to submission and as needed, during the review process

Thank you!

Questions, comments, concerns:

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